Pharmaceutical Drug Development

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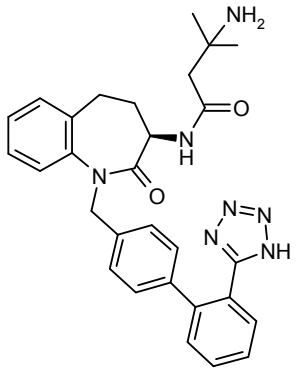
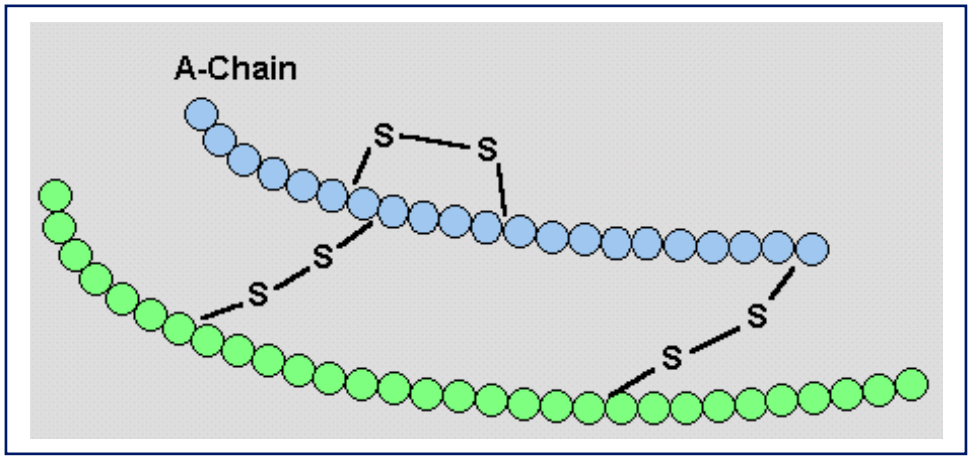
Agenda

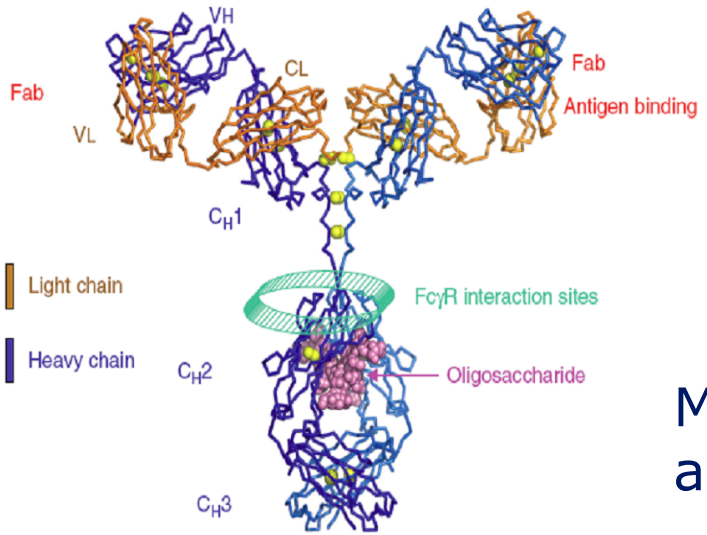
- 13.00-13.45: Pharmaceutical drug development
- 13.45-14.00: Break
- 14.00-14.45: Drug attrition
- 14.45-15.00: Break
- 15.00-16.00: Exercise

Pharmaceutical drugs are different

Small molecules







Proteins for replacement therapy

Monoclonal antibodies

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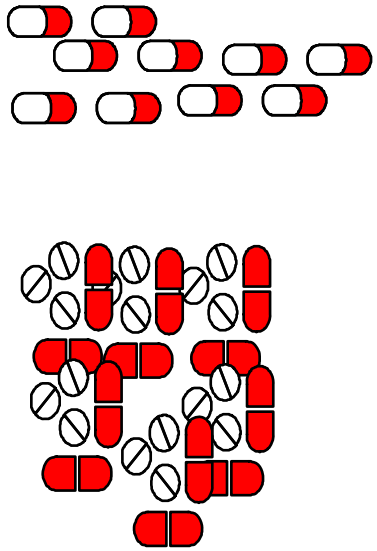
Administration of drugs is different

Oral administration



Administration by injections

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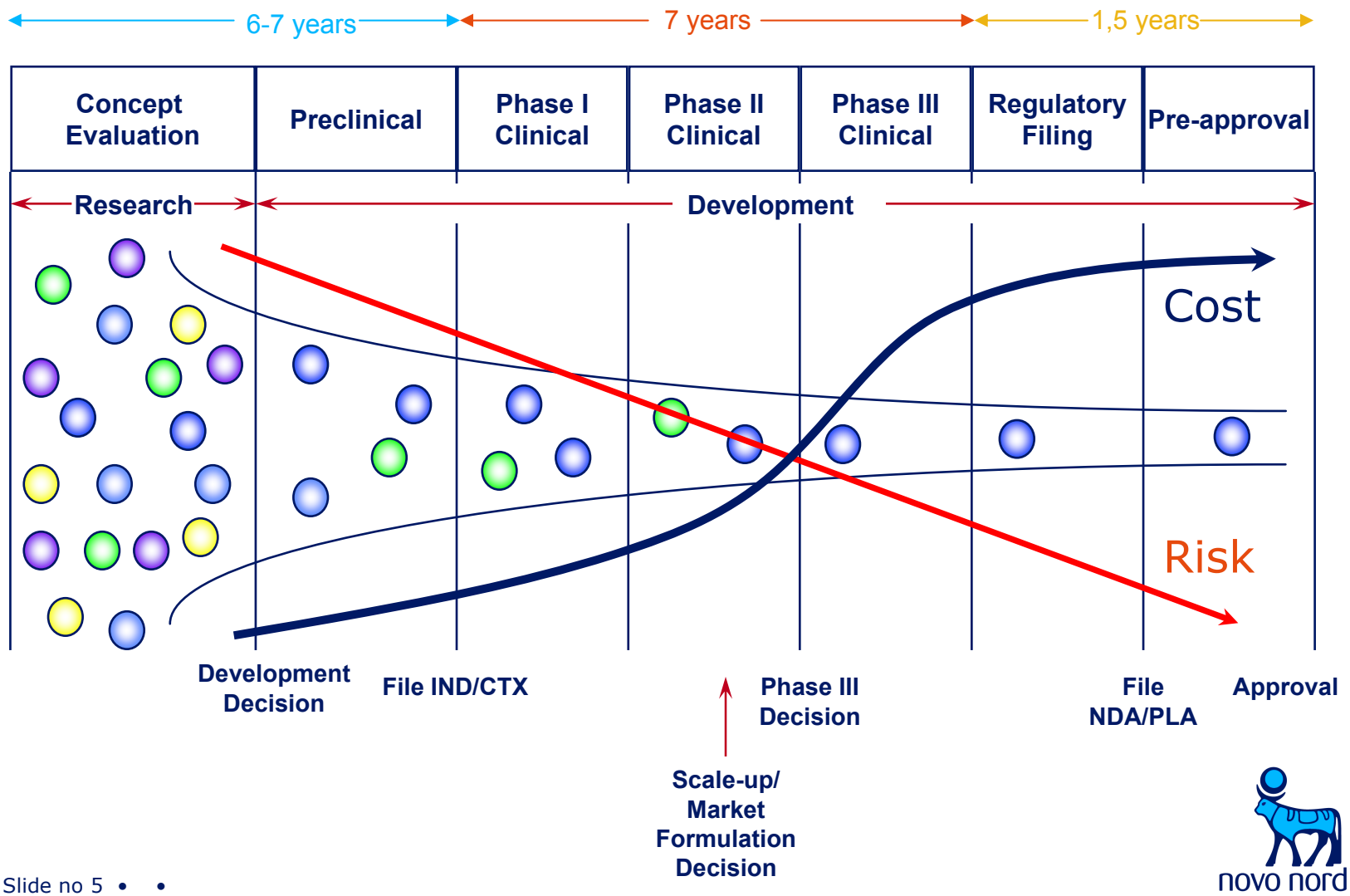
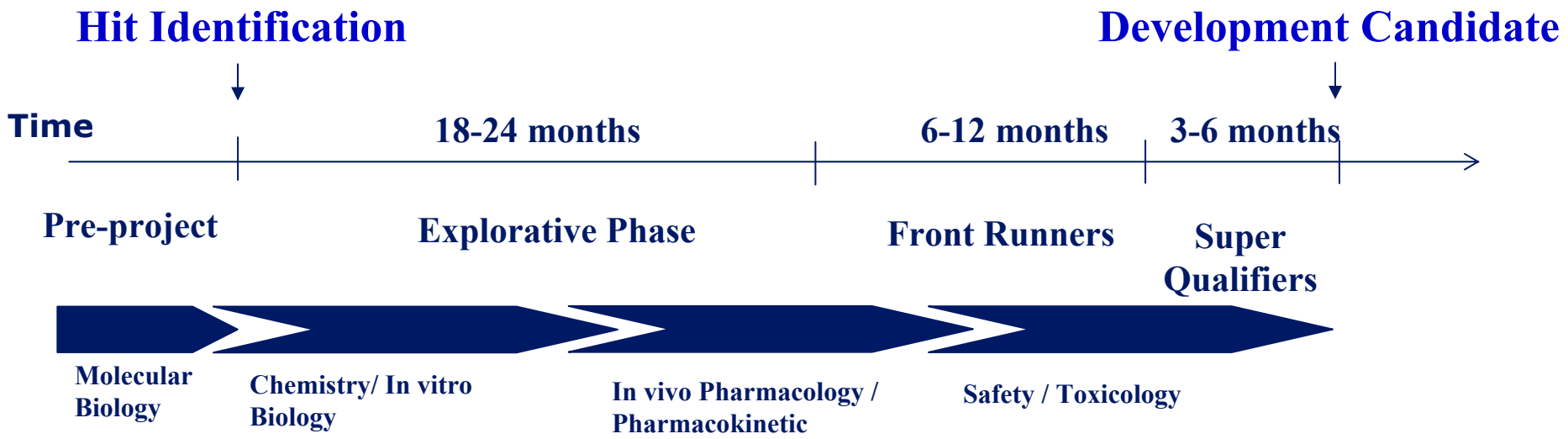
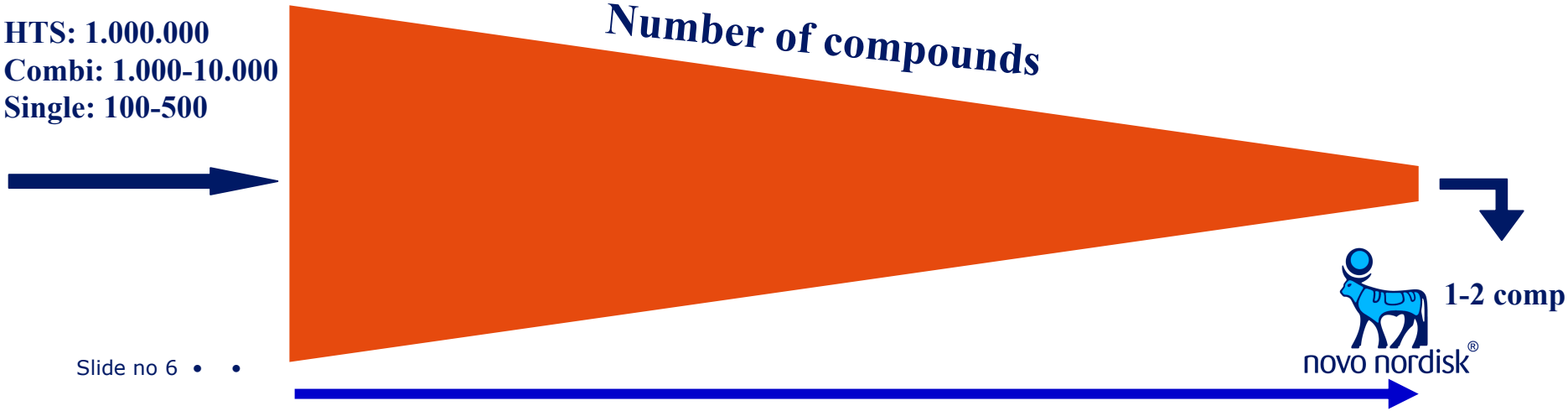
Pharmaceutical drug development overall



Typical small molecule drug discovery phases





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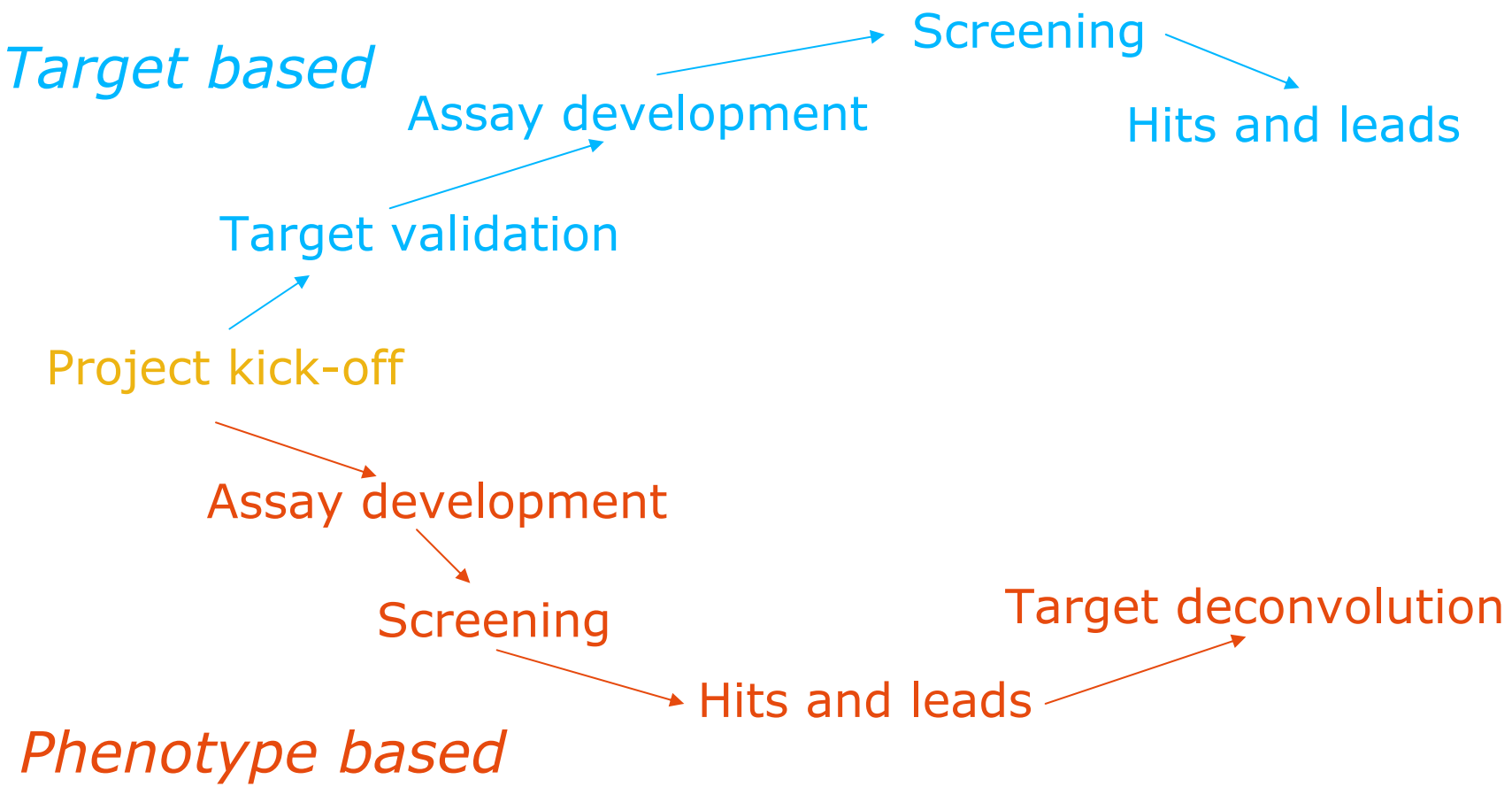
Drug discovery early stages



Target validation

- Disease tissue expression

1) Localisation of target in disease-relevant area & regulation of target expression

- Modulation in vitro

1. RNA knockouts (RNAi, antisense) & gene knockouts (antisense, ribozymes, zinc fingers)
2. Change of protein (antibodies, RNA, aptamers, peptides, dominant negative/wildtype protein)

- Modulation in vivo

1. Knockout models (but embryonic lethality & redundancy problems)
2. Transgenic mice

- Clinical proof of concept

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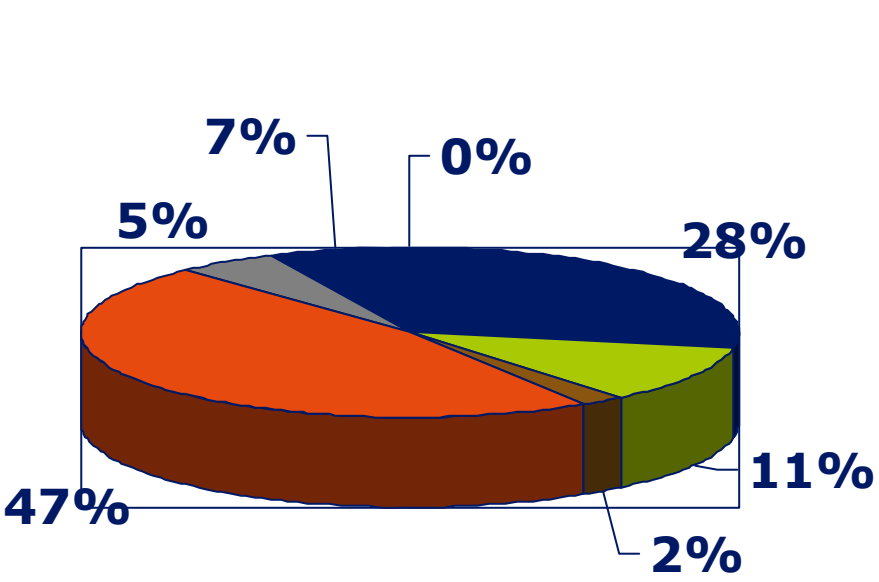
Therapeutic target classes



Adapted from Science 2000

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Value chain of drug discovery

- Target finding
- Lead finding (diversity)
- Optimization of affinity and selectivity
- Optimization of solubility
- Optimization of pharmacokinetic properties

A good drug candidate

- high in vitro potency
- high in vitro selectivity
- high in vivo potency
- good oral bioavailability
- low hepatic turnover/low clearance
- low or no interaction with CYP450
- no adverse effect/good safety
- ….

Pharmacodynamic

Pharmacokinetic

Safety/ toxicol.

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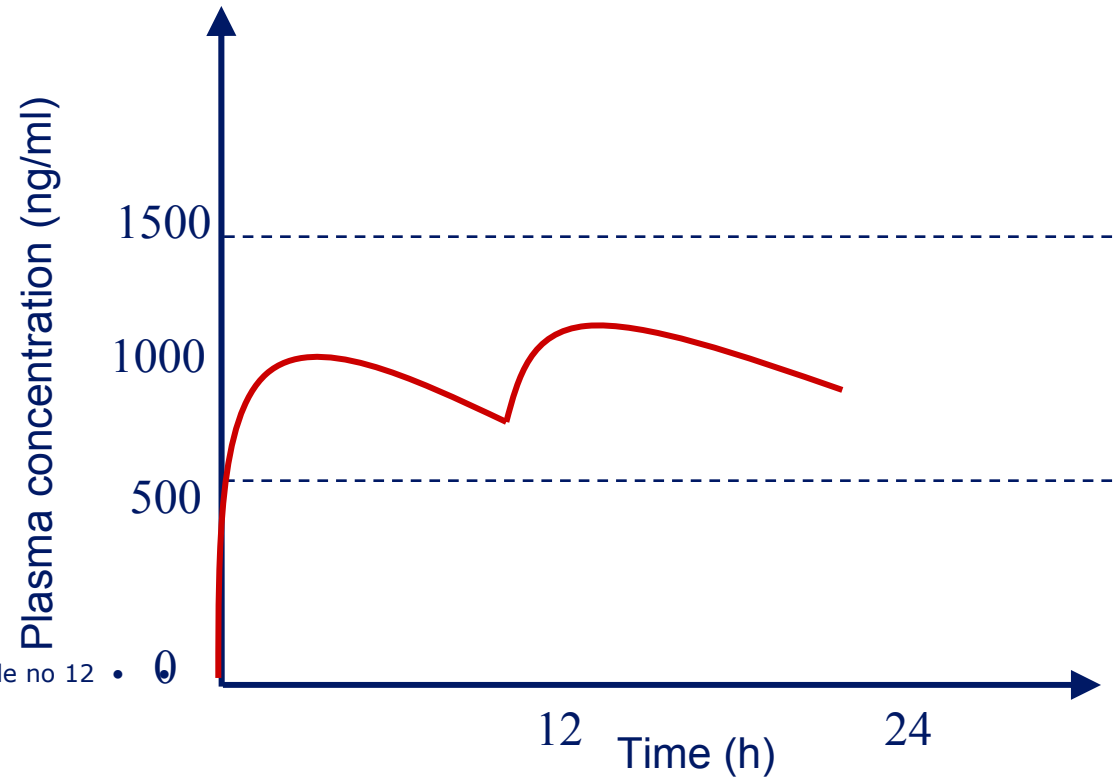
'Drugability'

- A drugable compound most be able to maintain therapeutically effective plasma levels with 1-2 times daily dosing PO



Adverse effects

Effect
(therapeutic window)

No effect

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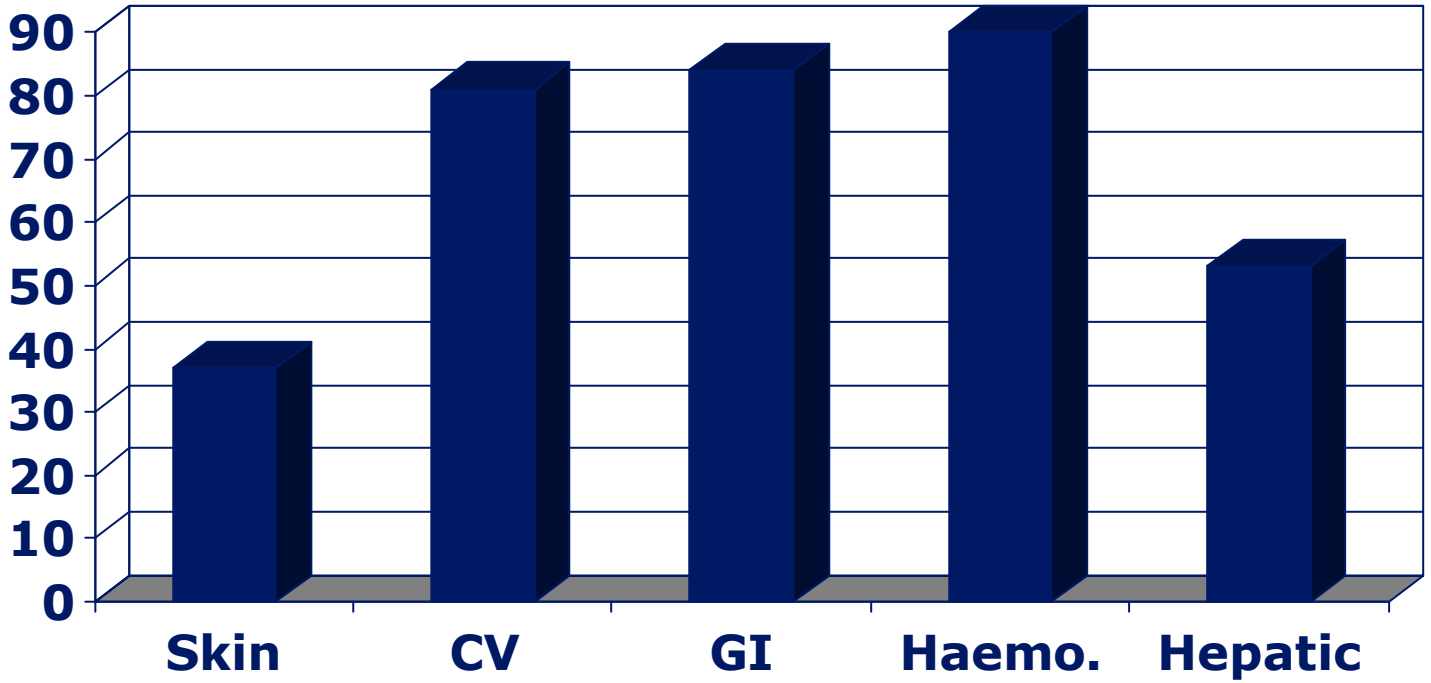
Preclinical safety evaluation

- Preclinical research and development using biological systems and animal models to explore intervention in the disease and to establish the preclinical safety profile of the therapeutic agent before early clinical trials in human subjects
- Determination of the potential for general toxicity

1. identification of target organs of toxicity (delayed effects, reversibility of effects, probability of occurrence)
2. identification of appropriate parameters to monitor in the clinic

- Characterization of the nature of the adverse effects
- Determination of the potential for specialized toxicity (reproductive and developmental, genetic, carcinogenic, immmunotox et.al.)
- Selection of appropriate doses for clinical trials (initial starting dose, dose-escalation scheme)
- Assessment of risk versus benefit in relation to clinical indication (normal volunteers, patients, identify at risk populations)

Percentage concordance between animal and human toxicities, grouped by organ.



Adapted from *Nature Reviews Drug Discovery* **3**, 226-236 (March 2004)

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Special biotechnology-derived pharmaceutical issues

- Species specificity

and the associated

- Detection and implications of altered immune status.

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Factors influencing the immunogenicity of biopharmaceuticals

- Sequence variation
- Glycosylation variation
- Contaminants and impurities from production
- formulation
- Route of administration, dose
- length of treatment
- patient characteristics
- unknown factors

Principles of drug testing prior to trials in humans

- Exact composition of drug should be known; if not, method of preparation
- Acute toxicity studies in animals of different species
- Chronic toxicity experiments at varying doses in different species for cumulative effects
- Careful and frequent observations of animals, to develop a composite picture of clinical effects
- Careful pathological examination of tissues with appropriate stains
- Effects of drugs on excretory or detoxifying organs, especially kidney and liver
- Rate of absorption and elimination, path and manner of excretion, concentration in blood and tissues at varying times
- Possible influence of other drugs and foodstuffs
- Careful examination for any untoward reactions

Clinical development

Pre-clinical	Animal expts	Pharmacodynamics Pharmacokinetics Toxicology
Clinical	Phase I Few healthy volunteers Phase II Few patients Phase III Many patients	Pharmacodynamics Pharmacokinetics Toxicology Efficacy Dosing + administration Side effects + interactions Controlled clinical trial
Post-marketing	Phase IV Many patients	Clinical experience

Development phases

Phase 1:

- First Human Dose
- Multiple Doses in Human Volunteers and patients
- Tolerability and safety
- Kinetic and dynamics and their relations (short surrogate markers)
- Bioavailability/ADME
- Clinical Proof of Principle
- Establishment of (a preliminary) therapeutic window – maximal tolerable dose , dose - response
- <100 persons (often healthy males)

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Development phases

Phase 2:

- Efficacy - dose-response
- Safety – efficacy (surrogate- markers ex. HbA_{1c})
- Longer term treatment (3 months)
- Selected patients (specific disease, otherwise healthy)
- 100 – 300 patients
- Placebo controlled

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Development phases

Phase 3a:

- Efficacy and safety during long-term treatment (1/2 –3 years)
- Patients and conditions like prescribed patients
- Comparative trials with active control
- 1000-3000 patients
- Pharmaco-economics
- Pharmacology: Interactions/special populations/ADME/ meal-test/mechanistic studies

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Development phases

Phase 3b:

- Positioning studies
- Special populations (children, pregnant, elderly…)
- Special medical scientific questions
- Support of treatment algorithms in special populations
- Comparative trials against competition

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Development phases

Phase 4:

- Post-approval
- New indications, line extension
- New knowledge about existing indications, special use
- Pharmacovigilance
- Safety surveillance
- Safety database/populations-surveillance
- Clinical experience trials

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Development phases

Exploratory phase

Target discovery & validation

Proof of concept clinical trials

Apply biomarkers and simulations
Demonstrate Proof of concept and dose selection

Confirmatory phase

Clinical trials

Apply innovative tools and clinical trial designs
Identify target patient population, confirm optimal dose and dosing regimen and establish the benefit/risk ratio

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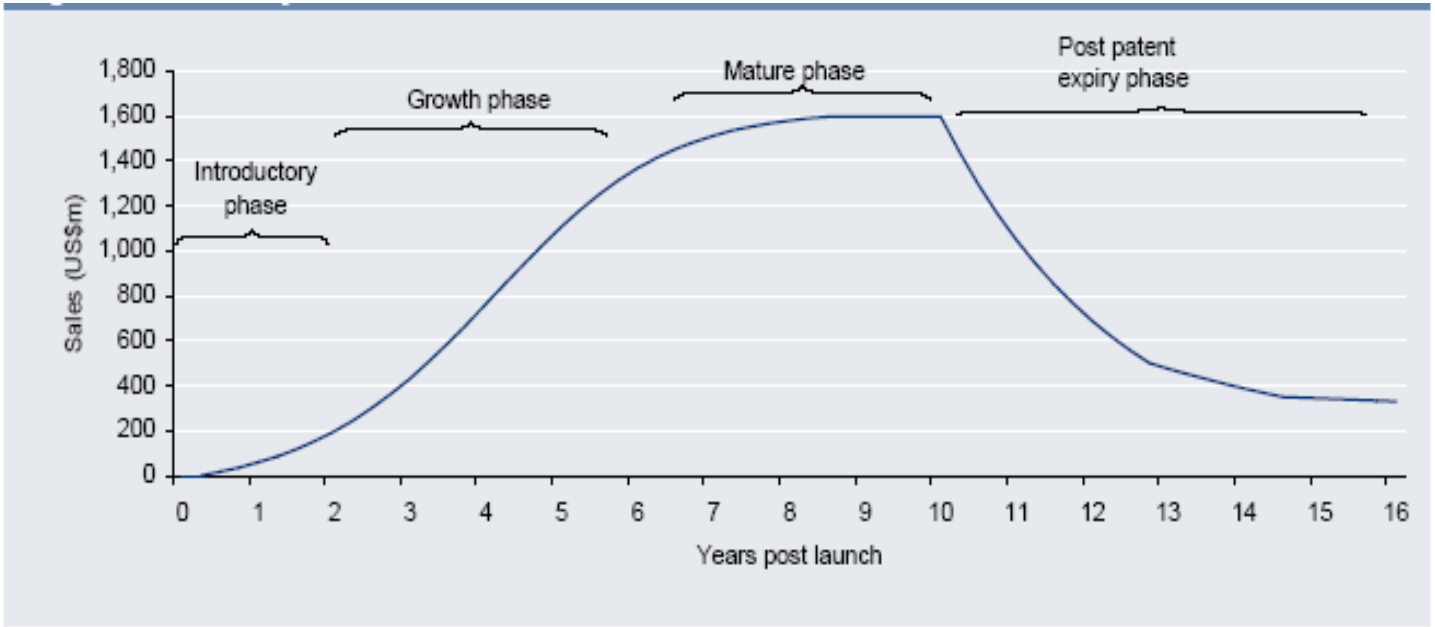
Product Lifecycle



Source: ING estimates

The environment is changing..

- New ”markets”
- Growing elderly population
- Increasing consumer power in the industrialized world
- Company strategies are different but new drug candidates in general are for chronic conditions in large populations & rely on premium prices
- Partnerships needed for ”neglected diseases”

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